Remarks

I. Support for Amendments and Status of the Claims

By the foregoing amendments, claims 2-5, 20-21, 29-49 and 51 are cancelled without prejudice to or disclaimer of the subject matter therein. New claims 52-57 are sought to be added. Support for the new claims can be found throughout the specification. Thus these new claims do not introduce new matter. Amendment is also sought to claims 1, 6-18, 22 and 28. These amendments are made to correct minor typographical errors, to better place the claims in a form for U.S. practice, and/or to incorporate subject matter from cancelled dependent claims. These amendments introduce no new matter, and their entry is respectfully requested. Upon entry of the foregoing amendments, claims 1, 6-19, 22-28, 50 and 52-57 are pending in the application, with claim 1 being the sole independent claim.

II. Summary of the Office Action

In the Office Action dated July 27, 2006 (hereinafter "the Office Action"), at page 2 the Examiner has alleged that Applicants' Information Disclosure Statement ("IDS") filed November 17, 2003, does not comply with 37 C.F.R. §§ 1.56 and 1.98, and has thus refused to fully consider this IDS.

At pages 2-3 of the Office Action, the Examiner has rejected claim 51 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite, and under 35 U.S.C. § 101, as allegedly providing an improper definition of a process. At pages 3-5 of the Office Action, the Examiner has rejected claims 50 and 51 under 35 U.S.C. § 112, first paragraph, as allegedly being not enabled. In making this rejection, the Examiner cites Schenk *et al.*,

Nature, 400:173-177, 1999 (hereinafter "Schenk"); Holtzman *et al.*, *Advanced Drug Delivery Reviews* 54:1603-1613, 2002 (hereinafter "Holtzman").

At pages 5-7 of the Office Action, the Examiner has rejected claims 15-18 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. At pages 7-8 the Examiner has rejected claim 22 under 35 U.S.C. § 112, first paragraph, as allegedly being not enabled. In making this rejection, the Examiner cites Bowie *et al*, *Science*, 247, (4948): 1306-1310.

At pages 8-11 of the Office Action, the Examiner has rejected claims 1-5, 19-23 and 50 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sebbel *et al* (US 6,964,769) (hereinafter "Sebbel") in view of Frenkel *et al., Proc. Natl. Acad. Sci. USA*, 97 (21): 11455-11459, 1999 (hereinafter "Frenkel"). At page 11 of the Office Action, the Examiner has rejected claims 4, 6-8, 11 and 13-18 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sebbel and Frenkel and further in view of Vasiljeva *et al*, FEBS Letters 431:7-11, 1998 (hereinafter "Vasiljeva"). At pages 11-12 of the Office Action, the Examiner has rejected claims 24-28 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sebbel and Frenkel and further in view of Robinson and Sauer, *Proc. Natl. Acad. Sci. USA 95: 5929-5934*, 1998 (hereinafter "Robinson and Sauer"). At page 12 of the Office Action, the Examiner has rejected claims 12 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sebbel, Frenkel and Vasiljeva and further in view of Golmohammadi *et al, Structure,* 4:543-554, 1996 (hereinafter "Golmohammadi").

In view of the following remarks, Applicants respectfully traverse the Examiner's rejections. Applicants therefore respectfully request that the Examiner reconsider and withdraw the rejections and allow the presently pending claims.

III. Information Disclosure Statement

At page 2 of the Office Action the Examiner has alleged that "[i]n view of the very low percentage of references material to patentability in the sampled documents reviewed, the [IDS is] not in compliance with 37 C.F.R. 1.56 and 1.98." Applicants respectfully disagree, and assert that the IDS does comply with 37 C.F.R. §§ 1.56 and 1.98.

Applicants note that neither the rules nor the MPEP requires a minimum "percentage of material references." Indeed, the MPEP states that:

> When in doubt, it is desirable and safest to submit information. Even though the attorney, agent, or applicant doesn't consider it material, someone else may see it differently and embarrassing questions can be avoided. The court in *U.S. Industries v. Norton Co.*, 210 USPQ 94, 107 (N.D. N.Y. 1980) stated "In short, the question of relevancy should be left the Examiner and not the Applicant." See also *LaBounty Mfg., Inc. v. U.S. Int'l Trade Comm'n*, 958 F.2d 1066, 22 USPQ2d 1025 (Fed. Cir. 1992).

MPEP § 2004, 8th ed., revised August 2006. Particularly in view of the MPEP's exhortation to submit information of even questionable materiality, Applicants' submissions therefore fully comply with the rules.

However, solely to advance prosecution, and not in acquiescence to the Examiner's objection, Applicants submit herewith a Second Supplemental IDS. Applicants respectfully submit that the accompanying IDS submission is not, and should not be construed as, an admission of materiality or an assertion of nonmateriality as to any of the information cited or not cited in the accompanying Second Supplemental IDS or in previous IDS submissions. Applicants respectfully request that the Examiner consider the accompanying IDS and documents cited therein and indicate such consideration by initialing forms PTO-SB/08A and PTO-SB/08B.

IV. Rejection under 35 U.S.C. § 112,second paragraph and under 35 U.S.C. § 101

At pages 2-3 of the Office Action, the Examiner has rejected claim 51 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner has further rejected claim 51 under 35 U.S.C. § 101, as allegedly providing an improper definition of the process. By the foreoing amendments, and for reasons unrelated to these rejections, Applicants have cancelled claim 51, thus rendering the rejections moot.

V. First Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement

At pages 3-5 of the Office Action, the Examiner has rejected claims 50 and 51 as allegedly failing to comply with the enablement requirement under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner states that "[T]he specification, while enabling for inducing anti-Abeta 1-6 antibodies capable of binding to amyloid plaques (page 9, 23 paragraph), does not provide enablement for a medicament, Office Action at page 4. As an initial matter, Applicants note that claim 51 has been cancelled, thus rendering moot this rejection as it may have been applied to claim 51. Applicants respectfully traverse the rejection of claim 50 on this ground.

In making the rejection, the Examiner asserts that:

> [P]hase II trial of active immunization by Elan Pharmaceuticals with amyloid beta (1-42) in humans led to the occurrence of CNS inflammation and, as a consequence, the trials were halted. Further, the cause of the inflammation was not known at the time of the invention.

Office Action at page 4.

In making this assertion, the Examiner refers to Holtzman which reported that human clinical trials for the treatment of Alzheimer's disease by active immunization with the so-

called AN1792 vaccine were suspended due to incidents of CNS inflammation (see Holtzman, page 1610, left column, last paragraph). To the extent that the Examiner is asserting that the claims are not enabled for such therapeutic uses, Applicants traverse this rejection on both legal and factual grounds. Applicants provide herewith Exhibit A, Gilman, S. *et al.*, "Clinical effects of Aβ immunization (AN1792) in patients with AD in an interrupted trial", *Neurology* 64:1553-1562 (2005) (hereinafter "Gilman") in support of these contentions.

First, the problems reported with the AN1792 vaccine, *i.e.*, a pre-aggregated synthetic Aβ1-42 preparation formulated with the adjuvant QS21, do not necessarily indicate that Applicants' compositions would cause similar problems. Indeed, Gilman states at page 1561, col. 1, that "prior to the initiation of [the AN1792 Phase II] study, there was no indication of meningoencephalitis in any preclinical investigations or during the phase I trials." Gilman goes on to suggest that polysorbate-80, which was absent from prior animal and human trials, but was added to the formulation used in the large phase II AN1792 trial reported in Holtzman "was instrumental in the development of the inflammatory reaction." Gilman, page 1561, col. 2. Thus, it is incorrect to presume that simply because the AN1792 vaccine trial reported in Holtzman led to significant adverse events, then Applicants' claimed compositions and methods are also *a priori* likely to produce serious adverse effects in humans.

Second, it does not follow that a vaccine that may cause adverse events (even serious ones) is not effective. However, Gilman, who analyzes the complete *actual* results of the clinical trials, reports that the data strongly indicate that the vaccine is effective in treating human Alzheimer's disease. Gilman concluded on page 1562, last paragraph, that:

> [A]lthough dosing in this trial was interrupted after fewer immunizations than were scheduled because of the occurrence of meningoencephalitis in a small percentage of immunized patients, the results offer promise for Aβ immunotherapy as a potential means of treating AD. The results showed significant effects in antibody reponders upon some memory functions as measured on the NTB, and the decreased CSF tau levels suggest a downstream neuropathological benefit of targeting Aβ. Together with postmortem reports of depleted neocortical Aβ in AN1792(QS21)-treated patients, the findings of this trial suggest that Aβ immunotherapy may be useful for the treatment of AD.

Therefore, contrary to the Examiner's position, those of ordinary skill in the art clearly believe that vaccination against Aβ is therapeutically effective for treating Alzheimer's disease.

Third, Applicants respectfully wish to remind the Examiner that a showing that a claimed composition or method is therapeutically effective and safe in humans is an inquiry specifically reserved for the FDA, not the USPTO, and is irrelevant to enablement or any other requirement for patentability. *See In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995). Therefore, the decision on whether an occurrence of CNS inflammation in a small subset of patients who were immunized is tolerable is ultimately that of the FDA, and is not relevant to patentability.

Fourth, and finally, Applicants respectfully wish to remind the Examiner of the proper standard by which animal models or *in vitro* experiments are held to be sufficient to enable claims to *in vivo* uses. The Federal Circuit has held that animal testing results are sufficient to establish whether one skilled in the art would believe that a pharmaceutical compound has an asserted clinical utility for the purposes of compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph. *Brana*, 51 F.3d at 1567-68. Furthermore, MPEP § 2164 states that:

> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of

> correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):
> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence (citations omitted).

Applicants note that the present specification provides abundant evidence that (i) the composition of the invention is capable of inducing high antibody response towards Aβ 1-6 (*see, e.g.*, Example 13, FIG. 2; and Example 20, FIG. 9) and the so-induced antibodies strongly cross-react with Aβ 1-40 (*see, e.g.*, Example 13, FIG. 3; and Example 21, FIG. 10) and with Aβ 1-42 (*see, e.g.*, Example 21, FIG. 10); (ii) the induced anti-Aβ 1-6 antibodies are capable of binding to amyloid plaques, as acknowledged by the Examiner (*see, e.g.*, Example 16, FIG. 4A and B; Example 19, FIG. 7A and B); (iii) mice immunized with the composition of the invention showed massive reduction of plaque density in neocortical and subcortical brain areas. Example 21 shows that, in a mouse model of Alzheimer's disease, both the median number of deposits and the total plaque area were highly significantly reduced between 80-98% compared to the PBS group in the cortex, caudate putamen, hippocampus, and thalamus ($p<0.001$ vs. PBS-group, Mann-Whitney test; FIG. 12). Example 22 shows that, in a therapeutic setting, the vaccine reduces plaque number in old mice with advanced stage of amyloid plaque pathology. Compared to the non-immunized group the median plaque number was reduced by 33% in the immunized group ($p<0.001$ vs PBS-group, Mann-Whitney test, FIGs. 15 and 16).

Thus in view of the foregoing evidence and remarks, Applicants assert that those of ordinary skill in the art would believe that the presently claimed compositions and methods have a therapeutic utility.

For at least these reasons, Applicants respectfully assert that the rejection under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement, has been overcome and request the reconsideration and withdrawal of the rejection.

VI. Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description

(a) In the Office Action at pages 5-7, the Examiner has rejected claims 15-18 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully traverse the Examiner's rejection.

In making this rejection, the Examiner contends that:

> [T]he application provides little, if any, guidance as to what modifications can be made to the peptides as to retain the ability to form the ordered and repetitive arrays. For these reasons, and as the application provides no operable species of the claim genera, much less a representative number, there is insufficient descriptive support in the application to demonstrate possession of the claimed genera of methods, involving the use of modified peptides to form an ordered and repetitive array..

Page 7 of the Office Action. The Examiner has also cited from section 2163 of the MPEP:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice.

Applicants respectfully disagree with the Examiner's contentions, and submit that the present specification provides a sufficient written description for the present claims, for at least several reasons.

First, the amino acid sequences of the coat proteins of the RNA phages that are recited in the present claims were known at the time of filing as indicated in the present application (*see*, for example, at page 14, paragraph 145 of the published US application 2004/0141984). Hence, the specific positions of the lysine residues within these amino acid sequences are also defined. Furthermore, as described in the present specification, page 16, paragraph 168:

> [T]he crystal structure of several RNA bacteriophages has been determined (Golmohammadi, R. et al., Structure 4:543-554 (1996)). Using such information, surface exposed residues can be identified and, thus, RNA-phage coat proteins can be modified such that one or more reactive amino acid residues can be inserted by way of insertion or substitution. As a consequence, those modified forms of bacteriophage coat proteins can also be used for the present invention.

Applicants further submit that sufficient description of a representative number of species was provided within the specification, as required by the *Eli Lilly* case cited in the MPEP at § 2163. At page 15, paragraph 153 of US2004/0141984 it states:

> Four lysine residues are exposed on the surface of the capsid of Qβ coat protein. Qβ mutants, for which exposed lysine residues are replaced by arginines can also be used for the present invention. The following Qβ coat protein mutants and mutant Qβ VLPs can, thus, be used in the practice of the invention: "Qβ-240" (Lys13-Arg; SEQ ID NO:17), "Qβ-243" (Asn 10-Lys; SEQ ID NO:18), "Qp-250" (Lys 2-Arg, Lys13-Arg; SEQ ID NO:19), "Qβ-251" (SEQ ID NO:20) and "Qβ-259" (Lys 2-Arg, Lys16-Arg; SEQ ID NO:21).

Furthermore, in Example 1 of the present application, the cloning, construction, expression and purification of the virus-like particle of Qβ comprising four of the aforementioned mutant coat proteins, respectively, were described. Despite the mutations of lysine residue at various locations of the Qβ coat protein, all these mutant coat proteins formed virus-like particle, suitable for the formation of a molecular antigen array.

Therefore, the present specification provides a sufficient written description for the present claims. This is further confirmed by a recent holding of the Federal Circuit that the disclosure of even a *single species* is sufficient written description of a claimed genus, if the specification also discloses methods of making and assaying other species of that genus without necessarily providing the nucleotide and/or amino acid sequences of those additional species. *See Invitrogen v. Clontech*, 429 F.3d 1052 (Fed. Cir. 2005).

Applicants thus assert that the disclosure of the present specification, viewed in the context of information that is readily available in the art, discloses a sufficient number of representative species of the invention as presently claimed. Hence, the present specification reasonably conveys to one skilled in the art that the inventors, at the time of filing, had possession of the presently claimed invention. Thus, claims 15-18 are fully described by the present specification, in compliance with the written description requirement of 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of the rejection therefore are respectfully requested.

VII. Second Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement

In the Office Action at pages 7-8, the Examiner has rejected claim 22 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled for SEQ ID NO:86. Applicants respectfully disagree. However, solely to advance prosecution, Applicants have deleted the recitation of SEQ ID NO:86 from claim 22, thus rendering the Examiner's rejection moot.

VIII. Rejections under 35 U.S.C. § 103

In the Office Action at pages 8-11, the Examiner has rejected claims 1-5, 19-23 and 50 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sebbel in view of Frenkel. As an initial matter, Applicants have cancelled claims 2-5 and 20-21, rendering the rejection of those claims moot. Applicants have also sought the amendment of claim 1. Applicants respectfully traverse the Examiner's rejection as it may be applied to the presently pending claims.

Applicants assert that the presently pending claims are not rendered obvious by Sebbel in view of Frenkel. Independent claim 1 is presently drawn, *inter alia*, to a

composition comprising an antigen or antigenic determinant that is an Aβ1-6 peptide, which associates to a virus-like particle of an RNA bacteriophage through at least one non-peptide bond.

Sebbel does not disclose, suggest or motivate the skilled person in the art to use *Aβ1-6 peptides* as antigens or antigenic determinants to associate with *a virus-like particle of an RNA-bacteriophage* to form an ordered and repetitive antigen array as required by present independent claim 1.

Moreover, Frenkel does *not* disclose or suggest immunization against amyloid beta peptide using a composition comprising a phage and *Aβ1-6 peptides*, as suggested by the Examiner on page 10 of the Office Action, but only describes genetically engineered *filamentous DNA bacteriophage*, presenting the *epitope EFRH, corresponding to amino acids 3-6*, either by (a) carrying the peptide YYEFRH *fused* (*i.e.*, via a peptide bond) to its minor coat protein gpIII; or (b) carrying the peptide VHEPHEFRHVALNPV *fused* (*i.e.*, via a peptide bond) to its major coat protein gpVIII. It is also important to note that the aforementioned peptides do *not* include the *Aβ1-6 peptide*. Thus, Frenkel does *not* disclose, nor suggest or motivate the skilled person in the art to use, *Aβ1-6 peptides* as antigens or antigenic determinants to associate through at least one *non-peptide bond* with *a virus-like particle of an RNA-bacteriophage* to form an ordered and repetitive antigen array as required by present independent claim 1. For at least these reasons, Sebbel and Frenkel, alone or in combination, do not teach all elements of the presently claimed invention.

At page 11 of the Office Action, the Examiner has rejected claims 4, 6-8, 11 and 13-18 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sebbel and Frenkel and further in view of Vasiljeva. Applicants respectfully traverse this portion of the rejection.

Vasiljeva mentions in passing the use of C-terminal UGA extension of the short from of Qβ coat, so-called A1 extension, as a target for presentation of foreign peptides on the outer surface of mosaic Qβ particles. However, only the five amino acid short preS1 epitope 31-DPAFR-35 of the hepatitis B surface antigen has been disclosed in Vasiljeva (see abstract of Vasiljeva). The short foreign peptide is expressed as a fusion protein (*i.e.*, via a peptide bond) with A1. There is nothing in the reference that discloses or suggests attaching such a five amino acid short peptide to the A1 extension using a *non-peptide* bond. Finally, there is nothing in the reference that discloses or suggests attaching *Aβ1-6 peptides* as antigens or antigenic determinants to form an ordered and repetitive antigen array. These deficiencies are not cured by the disclosures of Sebbel and/or Frenkel, for at least the reasons discussed hereinabove. Hence, for at least these reasons, Sebbel and Frenkel and Vasiljeva, alone or in combination, do not teach all elements of the presently claimed invention.

At pages 11-12 of the Office Action, the Examiner has rejected claims 24-28 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sebbel and Frenkel and further in view of Robinson and Sauer. At page 12 of the Office Action, the Examiner has rejected claims 12 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sebbel, Frenkel and Vasiljeva and further in view of Golmohammadi. Applicants have cancelled claims 4 and 5, rendering rejection to those claims moot. Applicants have amended claims 6-10, and respectfully traverse this portion of the rejection as it may be applied to presently pending claims.

Robinson and Sauer study the role of linker design such as linker length and linker composition in determining the stability and folding kinetics of single-chain proteins (see

abstract). Golmohammadi discloses the crystal structure of bacteriophage Qβ at 3.5 A resolution and the details of protein-protein interactions therein.

For reasons elaborated above, which are entirely incorporated herein by reference, Sebbel and Frenkel would not have rendered the present claims obvious under 35 U.S.C. § 103. The defects in these references cannot be remedied by Robinson and Sauer or Golmohammadi, alone or in combination.

Finally, the Examiner has not met the burden of demonstrating why one of ordinary skill in the art would have been motivated to combine these cited documents. If a combination of references is used to demonstrate obviousness, there must be "a reason, suggestion, or motivation in the prior art that would lead one of ordinary skill in the art to combine the references, and that would also suggest a reasonable likelihood of success." *Smiths Indus. Med. Sys., Inc. v. Vital Signs, Inc.*, 183 F.3d 1347, 1356 (Fed. Cir. 1999). "Such a suggestion or motivation may come from the references themselves, from knowledge by those skilled in the art that certain references are of special interest in a field, or even from the nature of the problem to be solved." *Id.* Although the references "need not expressly teach that the disclosure contained therein should be combined, the showing of combinability must be 'clear and particular.'" *Ruiz v. A.B. Chance*, 234 F.3d 654, 665 (Fed. Cir. 2000). A rigorous application of the requirement for showing a suggestion or motivation to combine references aids in avoiding an impermissible hindsight reconstruction of the claimed invention. *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999). As the Examiner has not provided a reason, suggestion, or motivation in the prior art that would have led one of ordinary skill in the art to combine the references, these references cannot be combined in an attempt to make out a *prima facie* case of obviousness of the presently pending claims.

For at least these reasons, the presently pending claims are not rendered obvious by the cited references, alone or in combination. Applicants respectfully request that the Examiner reconsider and withdraw the present rejection under 35 U.S.C. § 103(a).

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply, and allowance of all pending claims, are respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Brian J. Del Buono
Attorney for Applicants
Registration No. 42,473

Date: November 27, 2006

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

Clinical effects of Aβ immunization (AN1792) in patients with AD in an interrupted trial

S. Gilman, MD, FRCP; M. Koller, MD, MPH; R.S. Black, MD; L. Jenkins, PhD; S.G. Griffith, MD, PhD, MRCP; N.C. Fox, MD, FRCP; L. Eisner, MD; L. Kirby, MD; M. Boada Rovira, MD; F. Forette, MD; and J.-M. Orgogozo, MD, for the AN1792(QS-21)-201 Study Team*

Abstract—*Background:* AN1792 (beta-amyloid [Aβ]1–42) immunization reduces Aβ plaque burden and preserves cognitive function in APP transgenic mice. The authors report the results of a phase IIa immunotherapy trial of AN1792(QS-21) in patients with mild to moderate Alzheimer disease (AD) that was interrupted because of meningoencephalitis in 6% of immunized patients. *Methods:* This randomized, multicenter, placebo-controlled, double-blind trial of IM AN1792 225 μg plus the adjuvant QS-21 50 μg (300 patients) and saline (72 patients) included patients aged 50 to 85 years with probable AD, Mini-Mental State Examination (MMSE) 15 to 26. Injections were planned for months 0, 1, 3, 6, 9, and 12. Safety and tolerability were evaluated, and pilot efficacy (AD Assessment Scale–Cognitive Subscale [ADAS–Cog], MRI, neuropsychological test battery [NTB], CSF tau, and Aβ42) was assessed in anti-AN1792 antibody responder patients (immunoglobulin G titer ≥ 1:2,200). *Results:* Following reports of meningoencephalitis (overall 18/300 [6%]), immunization was stopped after one (2 patients), two (274 patients), or three (24 patients) injections. Of the 300 AN1792(QS-21)-treated patients, 59 (19.7%) developed the predetermined antibody response. Double-blind assessments were maintained for 12 months. No significant differences were found between antibody responder and placebo groups for ADAS–Cog, Disability Assessment for Dementia, Clinical Dementia Rating, MMSE, or Clinical Global Impression of Change, but analyses of the z-score composite across the NTB revealed differences favoring antibody responders (0.03 ± 0.37 vs -0.20 ± 0.45; $p = 0.020$). In the small subset of subjects who had CSF examinations, CSF tau was decreased in antibody responders (n = 11) vs placebo subjects (n = 10; $p < 0.001$). *Conclusion:* Although interrupted, this trial provides an indication that Aβ immunotherapy may be useful in Alzheimer disease.

NEUROLOGY 2005;64:1553–1562

Immunization with aggregated human beta amyloid (Aβ)1–42 (AN1792) has been used as an immunotherapeutic approach to stimulate clearance of amyloid plaques in APP transgenic mice that exhibit CNS pathology similar to the features characteristic of Alzheimer disease (AD).[1] Immunization of PDAPP mice reduced the development or progression of amyloid plaques and prevented the expected cognitive decline.[2-6] The efficacy of immunization with AN1792 in the PDAPP mouse model supports this approach as a therapeutic strategy targeting Aβ deposits in AD.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the May 10 issue to find the title link for this article.

After extensive preclinical studies in several species, the safety and tolerability of AN1792 in combination with the adjuvant QS-21 was evaluated in patients with AD. Phase I studies demonstrated that the optimal dose combination for eliciting an anti-

See also page 1563

*Members of the AN1792(QS-21)-201 Study Team are listed in the Appendix.

From the Department of Neurology (Dr. Gilman), University of Michigan, Ann Arbor; Elan Pharmaceuticals (Drs. Koller and Griffith), San Diego, CA; Wyeth Pharmaceuticals (Drs. Black and Jenkins), Collegeville, PA; Dementia Research Centre (Dr. Fox), Institute of Neurology, Queen Square, London, UK; Baumel-Eisner Neuromedical Institute (Dr. Eisner), Fort Lauderdale, FL; Pivotal Research Centers (Dr. Kirby), Peoria, AZ; Fundació ACE (Dr. Boada Rovira), Institut Català de Neurociències Aplicades, Barcelona, Spain; Hôpital BROCA La Rochefoucauld (Dr. Forette), Paris, France; and Department of Neurology (Dr. Orgogozo), Université de Bordeaux 2, CHU Pellegrin, Bordeaux, France.

Sponsored by Elan Pharmaceuticals, Inc. and Wyeth Research. N.C.F. holds a Medical Research Council Senior Clinical Fellowship.

Drs. Fox, Forette, and Orgogozo have received honoraria (in excess of $10,000 for Dr. Orgogozo only) from Wyeth Research. Drs. Fox and Orgogozo have also received honoraria from Elan Pharmaceuticals, Inc. Dr. Orgogozo is a consultant for Elan Pharmaceuticals, Inc. and Wyeth Research. Dr. Kirby has received grants in excess of $10,000 from Elan Pharmaceuticals, Inc. Dr. Gilman served as Chair of the Safety Monitoring Committee for the trial and received payment from Elan Pharmaceuticals, Inc., only for his time reviewing safety data. Drs. Griffith and Koller are employees of Elan Pharmaceuticals, Inc., and hold equity in excess of $10,000 in its parent company, Elan Corporation, plc. Drs. Jenkins and Black are employees of, hold equity in excess of $10,000, and have received honoraria in excess of 10,000 from Wyeth Research.

Presented in part at the 9th International Conference on AD; July 17–22, 2004; Philadelphia, PA.

Received August 12, 2004. Accepted in final form January 31, 2005.

Address correspondence and reprint requests to Dr. S. Gilman, Department of Neurology, University of Michigan, 300 N. Ingalls 3D15, Ann Arbor, MI 48109-0489; e-mail: sgilman@umich.edu

AN1792 antibody response was AN1792 225 μg and QS-21 50 μg.[7] Accordingly, this double-blind, placebo-controlled, multicenter phase IIa study was initiated to evaluate the safety, tolerability, and pilot efficacy of AN1792(QS-21) in patients with mild to moderate AD. The study was originally designed with two primary efficacy endpoints: to compare the change in whole brain volume as determined by serial MRI (Fox et al. 2004, submitted) and to evaluate cognitive change as measured using the AD Assessment Scale–Cognitive Subscale (ADAS–Cog) in patients who developed an antibody response to AN1792(QS-21) vs placebo. After the first reports of meningoencephalitis,[8] study drug administration was permanently discontinued, and the protocol was amended to monitor all patients for at least 9 months after the last dose of study drug while maintaining the blind. The objectives of the study were also amended such that the sole revised primary objective was to determine the safety and tolerability of AN1792(QS-21). Efficacy measures were also assessed, as they are important research outcomes for this and future AD studies.

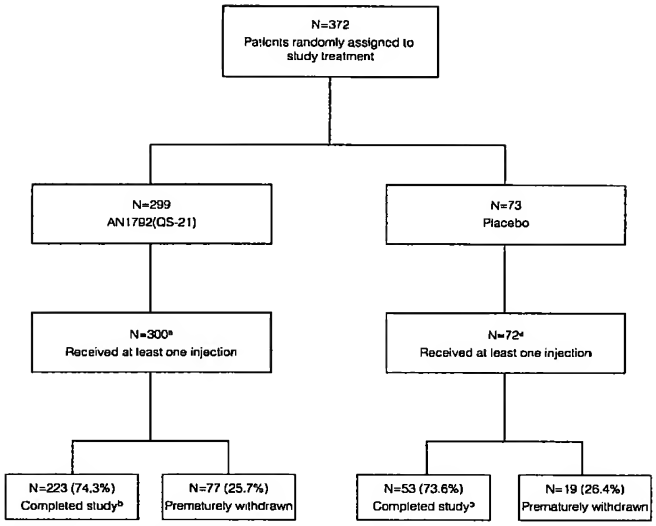

Figure 1. Patient disposition. [a]One patient randomized to the placebo group received AN1792(QS-21) due to a dosing error; [b]completers were defined as those patients who completed the study in accordance with the revised protocol.

Methods. *Patients.* Eligible patients were 50 to 85 years of age, met the criteria for a diagnosis of probable AD as defined by the National Institute of Neurologic and Communicative Disorders and Stroke–AD and Related Disorders Association,[9] and had an MRI brain scan supporting the clinical diagnosis of AD. Additional inclusion criteria were a score of 15 to 26 on the Mini-Mental State Examination (MMSE[10]), a Rosen-Modified Hachinski Ischemic score of ≤4, and written, informed consent from the patient and the patient's caregiver for the original protocol and subsequent amendments. Patients were excluded if they had clinically significant neurologic disease, other than AD, that might affect cognition; a major psychiatric disorder, systemic illness, or symptoms that could affect the patient's ability to complete the study; a Hamilton Psychiatric Rating Scale for Depression score of >12; used anticonvulsant, antiparkinsonian, anticoagulant, narcotic, or immunosuppressive medications within 3 months prior to baseline; used medication with the potential to affect cognition (unless maintained on a stable low to moderate dose regimen for at least 3 months prior to baseline); or used medications for cognitive enhancement other than a stable dosing regimen of an acetylcholinesterase inhibitor (≥6 months).

Study design and treatment. This randomized, placebo-controlled, double-blind, phase IIa clinical trial was conducted at 28 centers in the United States and Europe between September 2001 and December 2002. A total of 372 patients with mild to moderate AD were randomly assigned in a double-blind manner to receive treatment with a suspension of AN1792 225 μg (Elan Pharmaceuticals, Inc., South San Francisco, CA) and QS-21 50 μg (Antigenics, Framingham, MA) containing 0.4% polysorbate-80, or normal saline (placebo) in a 4:1 ratio. Randomization was performed by an independent statistician using a computerized, random-number generator and treatment was assigned by a central computer. Randomization was stratified by acetylcholinesterase inhibitor use (yes or no) and baseline MMSE score (15 to 20 or 21 to 26).

In each group, treatment was administered as a single 0.5 mL IM injection into the deltoid muscle and, according to the original protocol, dosing was planned to occur on day 0 and at months 1, 3, 6, 9, and 12 during the 15-month study. Patients in the active treatment group who had not developed a predefined serum anti-AN1792 antibody titer (IgG total tier > 1:2,200) were to be discontinued at month 8, after administration of four injections. Due to the premature discontinuation of the immunization, patients received only one to three injections. All patients enrolled in the study (including those who had previously discontinued early) were invited to participate in the safety follow-up period, which continued blinded and lasted for at least 9 months after their last dose of study treatment. Assessments were performed at weeks 1, 2, and 4, and thereafter at monthly intervals (with additional visits at months 3.5 and 6.5) until month 12 or early termination.

Site-specific local independent ethics committees approved the original protocol, amendments, and related informed consent forms prior to implementation. The study was conducted in accordance with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and in compliance with the Declaration of Helsinki 1964 as modified in October 2000.[11] An eight-member independent Data Safety Monitoring Committee assessed the safety of the study drug throughout the trial.

Outcome measures. The protocol was amended following the occurrence of meningoencephalitis such that cognitive outcomes were reduced to secondary measures, as safety and tolerability became the primary outcome measures of the study. The primary outcome measures were monitored throughout the trial by adverse event (AE) reporting, physical and neurologic examinations, injection site reactions, vital signs, and laboratory evaluations (biochemical and hematologic tests and urinalyses). Physical and neurologic assessments, an ECG, and an MRI brain scan were performed at screening and the final visit. Vital signs were evaluated at each visit.

An ELISA was used to determine anti-AN1792 immunoglobulin (Ig) G (total) and IgM levels in serum and CSF samples. The ELISA had a lower limit of detection of 1:25 for CSF IgG, CSF IgM, and serum IgM, and a lower limit of detection of 1:50 for serum IgG. Serum was collected at approximately monthly intervals, and CSF was collected in a subset of patients at baseline and month 12. Antibody responders were predefined as serum anti-AN1792 IgG (total) titer ≥1:2,200 at any time after injection 1. This titer was selected as the minimum anti-Aβ titer predicted to be of clinical benefit, based on preclinical data (Elan Pharmaceuticals, Inc., data on file).

Predefined secondary evaluations included the following cognitive and functional tests at baseline, month 6, and month 12: MMSE, score range 0 to 30;[10] ADAS–Cog, score range 0 to 70;[12] AD Cooperative Study–Clinical Global Impression of Change (ADCS–CGIC), seven-point scale;[13] Disability Assessment for Dementia (DAD), score range 0 to 100%;[14] Clinical Dementia Rating (CDR) scale,[15] score range 0 to 3; and a Neuropsychological Test Battery (NTB). The NTB consisted of the following nine components: Wechsler Memory Visual–Immediate (WMVis-I, score range 0 to 18); Wechsler Memory Verbal–Immediate (WMVer-I, 0 to 24); Rey Auditory Verbal Learning–Immediate (RAVL-I, 0 to 105); Wechsler Memory–Digit Span (WMDS, 0 to 24); Controlled Word Asso-

Table 1 Patient demographics, baseline characteristics, and medications

		AN1792(QS-21)		
	Placebo, n = 72	Responder, n = 59	Nonresponder, n = 241	Total, n = 300
Mean age ± SD (range), y	71.0 ± 8.3	72.5 ± 6.9	72.4 ± 8.1	72.4 ± 7.8
	(52.7–85.9)	(53.1–83.9)	(50.1–85.7)	(50.1–85.7)
Male:female, n (%)	29:43	27:32	111:130	138:162
	(40.3:59.7)	(45.8:54.2)	(46.1:53.9)	(46.0:54.0)
Mean weight ± SD (range), kg	67.3 ± 13.1	65.9 ± 12.5	68.2 ± 13.1	67.8 ± 13.0
	(43.0–110.8)	(41.3–114.7)	(34.5–111.7)	(34.5–114.7)
White, n (%)	69 (95.8)	54 (91.5)	227 (94.2)	281 (93.7)
Mean duration of AD ± SD (range), y	3.9 ± 1.9	3.8 ± 1.9	3.6 ± 2.0	3.7 ± 1.9
	(1.0–8.0)	(1.0–10.0)	(1.0–11.0)	(1.0–11.0)
Family history of AD, n (%)	28 (38.9)	25 (42.4)	103 (42.3)	127 (42.3)
Previous AChEI use, n (%)	62 (86.1)	48 (81.4)	197 (81.7)	245 (81.7)
Mean MMSE scores (SD)	20.2 (3.5)	20.5 (3.3)	20.4 (3.4)	20.4 (3.3)
Mean Rosen-Modified Hachinski Ischemic total score* (SD)	0.6 (0.7)	0.4† (0.6)	0.4† (0.7)	0.4† (0.6)
APOE ε4 allele status, n (%)				
No ε4 alleles	29 (41.4)	19 (33.3)	86 (36.9)	105 (36.2)
One ε4 allele	36 (51.4)	33 (57.9)	99 (42.5)	132 (45.5)
Two ε4 alleles	5 (7.1)	5 (8.8)	48‡ (20.6)	53† (18.3)
Baseline medications, n (%)				
Donepezil	45 (62.5)	34 (57.6)	142 (58.9)	176 (58.7)
Galantamine	3 (4.2)	6 (10.2)	13 (5.4)	19 (6.3)
Rivastigmine	14 (19.4)	11 (18.6)	42 (17.4)	53 (17.7)
Hormone replacement therapy	13 (18.1)	11 (18.6)	27 (11.2)	38 (12.7)
Vitamin E	24 (33.3)	15 (25.4)	70 (29.1)	85 (28.3)
No. injections, n (%)				
1	2 (2.8)	2 (3.4)	0 (0.0)	2 (0.7)
2	64 (88.9)	46 (78.0)	228 (94.6)	274 (91.3)
3	6 (8.3)	11 (18.6)	13 (5.4)	24 (8.1)

Patients were considered antibody responders if they had a serum anti-AN1792 IgG (total) titer ≥ 1:2200 at any time after injection 1.

* Possible score of 0–12; scores ≤4 in dementia patients are suggestive of a nonischemic etiology.
† $p < 0.05$ vs placebo, two-sample t test; ‡ $p < 0.05$ vs placebo, Fisher's exact test.

AD = Alzheimer disease; AChEI = acetylcholinesterase inhibitor; MMSE = Mini-Mental State Examination.

ciation Test (COWAT); Category Naming Test (CNT); Wechsler Memory Visual–Delayed (WMVis-D, 0 to 6); Wechsler Memory Verbal–Delayed (WMVer-D, 0 to 8); and Rey Auditory Verbal Learning–Delayed (RAVL-D, 0 to 30). The cognitive scales were administered by two blinded raters: the first administered the ADAS–Cog, DAD, and NTB; the second administered the ADCS–CGIC and CDR. In addition to assessments of individual component scores, raw scores on each of the nine NTB tests were converted to z-scores using the sample baseline mean and SD for each test. The resultant z-scores were averaged to obtain a composite z-score including all nine NTB tests. The NTB was further explored by subgrouping the overall composite NTB z-score into immediate memory (WMVis-I, WMVer-I, RAVL-I), delayed memory (WMVis-D, WMVer-D, RAVL-D), executive function (WMDS, COWAT, CNT), and all memory (all six memory tests) composite z-scores. Change from baseline was calculated as the post-baseline composite z-score minus the baseline score, such that a positive change indicates an improvement from baseline. Each of the five composite NTB measures was analyzed using analysis of covariance with change from baseline z-score as the response and baseline value as the covariate, with the same adjustments as in the principal analysis. In addition to the cognitive tests, ELISA determinations of CSF tau and Aβ42 protein,[16] and brain, hippocampal, and ventricular volume, as determined by MRI (reported elsewhere [Fox et al. 2004, submitted]), were analyzed.

Statistical analysis. Sample sizes and power calculations were generated according to the original primary endpoints of the study (whole brain volume determined by MRI and cognitive change as determined by ADAS–Cog) using a two-sided test at the 5% level of significance. Based on MRI data,[17] a sample size of 75 patients per group would provide 78% power to detect a 30% change in rate of reduction of whole brain volume (placebo vs active). Additionally, a sample size of 75 patients per group would provide 63% power based on an ADAS–Cog three-point difference (placebo vs active) in annualized mean change and an SD of eight points. Both estimates assume that analysis would compare the placebo group to the "antibody responder" patients from the active group. Based on data from a previous phase I study in elderly AD

Table 2 Number (%) of patients with treatment-emergent adverse events reported during treatment with AN1792(QS-21) or placebo

Event	Placebo, n = 72	AN1792(QS-21) Responder, n = 59	AN1792(QS-21) Nonresponder, n = 241	AN1792(QS-21) Total, n = 300
Adverse events	59 (81.9)	51 (86.4)	215 (89.2)	266 (88.7)
Treatment-related	8 (11.1)	22 (37.3)	55 (22.8)	77 (25.7)
Mild	6 (8.3)	4 (6.8)	33 (13.7)	37 (12.3)
Moderate	2 (2.8)	5 (8.5)	11 (4.6)	16 (5.3)
Severe	0 (0.0)	13 (22.0)	11 (4.6)	24 (8.0)
Serious adverse events				
Non-fatal	9* (12.5)	21 (35.0)	44*† (18.3)	65*† (21.7)
Treatment-related	0 (0.0)	13 (22.0)	9† (3.7)	22† (7.3)
Death	2 (2.8)	1* (1.7)	4†‡ (1.7)	5*†‡ (1.7)
Clinically important abnormal laboratory values	9 (12.5)	6 (10.2)	29 (12.0)	35 (11.7)

Patients were considered antibody responders if they had a serum anti-AN1792 IgG (total) titer ≥ 1:2200 at any time after injection 1.

* One additional patient (not recorded in the table) died from progression of AD after the end of the study follow-up period.
† One death (cerebral infarct) was considered to be related to study treatment.
‡ One additional patient (not recorded in the table) died secondary to aspiration after the end of the study follow-up period.

AD = Alzheimer disease.

patients treated with AN1792(QS-21),[7] it was estimated that approximately 25% of patients would develop serum anti-AN1792 titers of ≥1:2,200 (defined as antibody responders). Accordingly, in order to achieve approximately 75 antibody responders, 300 patients were planned for enrollment into the active group and 75 patients for the placebo group.

AEs were evaluated in all patients who were randomized and received at least one injection of study drug (safety population). Geometric mean serum anti-AN1792 titers (and 95% CI) were calculated for all visits at which titers were assessed for the antibody responder and placebo groups.

As it was anticipated that only 25% of active patients would become antibody responders, the prespecified efficacy analyses were conducted on the efficacy-evaluable population, rather than on an intent-to-treat (ITT) population. The efficacy-evaluable population consisted of antibody responders and placebo patients, i.e., 1) all patients injected with AN1792(QS-21) who had a baseline ADAS–Cog evaluation, an anti-AN1792 IgG (total) serum titer ≥1:2,200 at any post-injection visit, and at least one post-injection ADAS–Cog evaluation; and 2) all patients injected with placebo who had a baseline ADAS–Cog efficacy evaluation and at least one post-injection ADAS–Cog evaluation.

The ADAS–Cog, DAD, CDR, and NTB subscales and CSF levels of tau and Aβ42 were analyzed using analysis of covariance with change from baseline as the response, baseline value as the covariate, and treatment and stratum (acetylcholinesterase inhibitor use [yes, no], MMSE score at screening [15–20, 21–26], and geographic location [Europe, United States]) as independent variables. The MMSE was analyzed using the same type model except that the MMSE score at screening was not included as a covariate. The Cochran–Mantel–Haenszel mean score test, stratified by acetylcholinesterase inhibitor use, MMSE score at screening, and geographic location, with equally spaced scores for the ordered levels of the response variable, was used to compare the ADCS–CGIC distributions for each treatment. In addition, all analyses were performed excluding encephalitis patients, and similar results were observed unless stated otherwise.

Results. *Patients.* A total of 372 patients were randomized to receive study treatment. One patient who had been randomly assigned to the placebo group received AN1792(QS-21) due to a dosing error (figure 1); this patient has been included in the AN1792(QS-21) group for all data summaries. Accordingly, 300 patients were treated with AN1792(QS-21) and 72 patients received placebo. Baseline characteristics and patient demographics were generally similar between the two study groups in both the safety and efficacy-evaluable populations (table 1). Patients in both the active and placebo groups had low mean Rosen-Modified Hachinski Ischemic total scores (suggesting a non-ischemic etiology of dementia); the scores were slightly lower (p = 0.004), but not clinically different, in the AN1792(QS-21) group in the safety population, and there was no difference between antibody responders and nonresponders. The majority of patients (>90%) received two of the planned six injections before the sponsors halted the study (see table 1). Of the 300 subjects who received AN1792(QS-21), 59 (19.7%) were antibody responders (i.e., developed a serum anti-AN1792 IgG (total) titer ≥1:2,200 at any time after injection 1).

Safety and tolerability. AEs were reported in 266/300 (88.7%) patients who received AN1792(QS-21) and 59/72 (81.9%) placebo-treated patients, and occurred with similar frequency in antibody responders and nonresponders (table 2). Treatment-related AEs, serious AEs (SAEs), and AEs leading to treatment discontinuation were more frequent in AN1792(QS-21) recipients than in placebo recipients, and occurred more frequently in antibody responders than in nonresponders. Deaths and clinically important abnormal laboratory values were no more common in AN1792(QS-21)-treated patients than in placebo patients (see table 2).

Adverse events. Table 3 summarizes the most frequently reported AEs. Infection (19%), headache (17.3%), diarrhea (9.7%), and encephalitis (6%) were reported more frequently (by ≥5%) among AN1792(QS-21) patients than in placebo recipients. Treatment-related AEs were reported in 77/300 (25.7%) patients in the AN1792(QS-21) group (22 responders and 55 nonresponders), of which 24/300 (8%) were reported as severe (see table 2) and the majority of these were associated with encephalitis.

Table 3 Number (%) of patients with adverse events (reported by ≥5% of patients in any group) during treatment with AN1792(QS-21) or placebo

		AN1792(QS-21)		
	Placebo, n = 72	Responder, n = 59	Nonresponder, n = 241	Total, n = 300
Accidental injury	11 (15.3)	5 (8.5)	36 (14.9)	41 (13.7)
Agitation	1 (1.4)	3 (5.1)	13 (5.4)	16 (5.3)
Anxiety	4 (5.6)	4 (6.8)	14 (5.8)	18 (6.0)
Asthenia	2 (2.8)	8 (13.6)	14 (5.8)	22 (7.3)
Back pain	6 (8.3)	1 (1.7)	18 (7.5)	19 (6.3)
Confusion	6 (8.3)	7 (11.9)	28 (11.6)	35 (11.7)
Depression	9 (12.5)	7 (11.9)	20 (8.3)	27 (9.0)
Diarrhea	3 (4.2)	6 (10.2)	23 (9.5)	29 (9.7)
Dizziness	4 (5.6)	4 (6.8)	17 (7.1)	21 (7.0)
Encephalitis	0 (0.0)	13 (22.0)	5 (2.1)	18 (6.0)
Flu syndrome	3 (4.2)	2 (3.4)	18 (7.5)	20 (6.7)
Hallucinations	4 (5.6)	3 (5.1)	6 (2.5)	9 (3.0)
Headache	7 (9.7)	15 (25.4)	37 (15.4)	52 (17.3)
Infection	9 (12.5)	10 (17.0)	47 (19.5)	57 (19.0)
Insomnia	3 (4.2)	6 (10.2)	9 (3.7)	15 (5.0)
Nausea	3 (4.2)	4 (6.8)	11 (4.6)	15 (5.0)
Pain	8 (11.1)	8 (13.6)	23 (9.5)	31 (10.3)
Rash	4 (5.6)	3 (5.1)	9 (3.7)	12 (4.0)
Any adverse event	59 (81.9)	51 (86.4)	215 (89.2)	266 (88.7)

Patients were considered antibody responders if they had a serum anti-AN1792 IgG (total) titer ≥ 1:2200 at any time after injection 1.

The most common treatment-related AEs were encephalitis, headache, and confusion. Encephalitis occurred exclusively ($p < 0.0001$) in the AN1792(QS-21) group (18/300, 6.0%) as described in detail elsewhere.[8] Thirteen of the 18 patients with encephalitis were classified as antibody responders, although the magnitude of antibody response was variable (see table E-1 on the *Neurology* Web site at www.neurology.org). Injection site reactions were reported in both groups; however, they tended to be more significant and of longer duration among patients treated with AN1792(QS21) vs placebo. Mild tenderness was the most common symptom.

Other SAEs. Non-fatal SAEs were reported in 74 patients (see table 2); however, separate SAEs that resulted in death (cerebral infarct, accidental injury, neoplasm) were also reported in 3 of these patients. Twenty-two patients developed 27 treatment-related SAEs (encephalitis [n = 18], encephalopathy [n = 2, one of which also had encephalitis], confusion [n = 2], grand mal convulsion [n = 1], retinal vein thrombosis [n = 1], cerebral hemorrhage [n = 1], convulsion [n = 1], and hemiplegia [n = 1]), all of whom received AN1792(QS-21). Of these events, 13 cases of encephalitis, 1 case of encephalopathy, and 1 case of grand mal convulsion were reported in anti-AN1792 responders. The overall incidence of cerebral hemorrhage reported during the study was low and similar between AN1792(QS-21) (2/300 [0.7%]) and placebo groups (1/72 [1.4%]).

Seven patients died during the study follow-up period, and the incidence of death was similar in the AN1792(QS-21) and placebo groups (1.7% [5/300] vs 2.8% [2/72]; see table 2). Deaths in the placebo group were caused by neoplasm or cerebral hemorrhage, and those in the AN1792(QS-21) group were due to myocardial infarction (n = 2), broken neck, progression of AD, or nonhemorrhagic cerebral infarct. With the exception of one event of myocardial infarction, all deaths in the AN1792(QS-21) group occurred in antibody nonresponders. Only the cerebral infarction (which occurred 205 days after the second dose of AN1792(QS-21) in a nonresponder patient without encephalitis) was considered by the investigator as related to study treatment. Two additional deaths occurred after the end of the study follow-up period. One antibody nonresponder patient died secondary to aspiration pneumonia 15 months after the second injection of AN1792(QS-21), and one antibody responder patient died from progression of AD 13 months after the third injection. Consent was given for a brain autopsy examination in both patients.[18,19]

Additional safety variables. There were no notable trends in biochemistry, hematology, urinalysis, blood pressure, or heart rate over time or between groups observed during the study. Although clinically significant EKG abnormalities were reported in eight patients treated with AN1792(QS-21), none were considered related to treatment.

Immunologic findings. Fifty-nine of the 300 patients (19.7%) treated with AN1792(QS-21) were antibody responders. The majority of these patients (47/59) received two injections of study drug before developing a positive

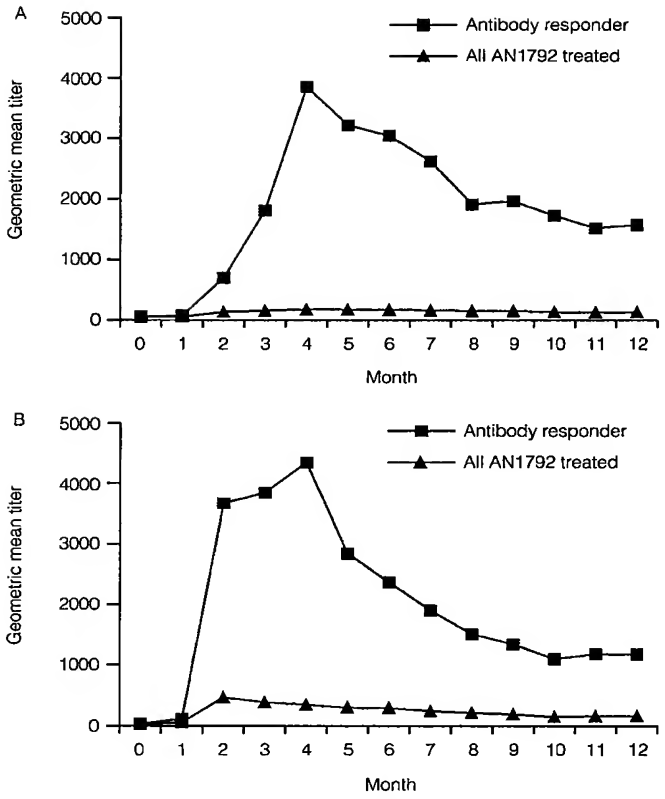

Figure 2. Geometric mean serum titers in patients immunized with AN1792(QS-21) in the safety (all treated, n = 300) and efficacy-evaluable (antibody responder, n = 59) populations. (A) Anti-AN1792 IgG (total); (B) anti-AN1792 IgM. Patients were considered antibody responders if they had a serum anti-AN1792 IgG (total) titer ≥1:2,200 at any time after injection 1. Data presented are the reciprocal of the geometric mean titer.

response (serum anti-AN1792 IgG [total] titer ≥1:2,200 at any time after injection 1); three patients developed positive responses after one injection and the remaining nine patients after three injections. In the safety population (figure 2), peak geometric mean serum anti-AN1792 titers in treated patients were 1:174 (month 4) for IgG and 1:469 (month 2) for IgM. In the efficacy-evaluable population (see figure 2), peak geometric mean serum anti-AN1792 titers in antibody responders occurred at month 4, and were 1:3,848 for IgG and 1:4,534 for IgM.

No significant differences in geometric mean serum anti-AN1792 IgG or IgM titers were observed between patients who developed encephalitis and those who did not (see table E-1). A higher percentage of the patients with encephalitis were antibody responders compared with AN1792(QS-21)-treated patients without encephalitis (13/18 [72.2%] vs 46/282 [16.3%]; $p < 0.0001$). Of the five antibody nonresponders who developed encephalitis, four showed peak anti-AN1792 IgG titers ≥1:100 (range 1:641 to 1:1,114) and peak anti-AN1792 IgM titers ≥1:100 (range 1:297 to 1:12,157); the fifth patient had peak IgM titer of 1:1,201, but no elevation of IgG titer.

Of the 57 AN1792(QS-21)-treated patients who consented to post-baseline CSF sampling, anti-AN1792 antibody (IgG or IgM) was detectable in the CSF of nine patients, five of whom were antibody responders (serum IgG ≥1:2,200). Of the nine patients with detectable CSF antibodies, four developed encephalitis (three serum antibody responders and one serum antibody nonresponder).

Cognitive function. There were no differences between treatment groups in cognitive, disability, and global change scores, as measured using the ADAS–Cog, DAD, CDR, MMSE, and ADCS–CGIC scales. These measures declined from baseline in antibody responders and placebo-treated patients during the course of the study follow-up period (table 4).

The results of the NTB revealed that antibody responders had an improvement compared with placebo in the WMVer-D scale ($p = 0.047$), and a small improvement from baseline in the WMDS scale ($p = 0.094$) (table 5). Mean adjusted change scores in the WMVis-I, WMVis-D, WMVer-I, RAVL-I, RAVL-D, COWAT, and CNT scales among antibody responders were not statistically different from those in placebo recipients.

Analysis of the nine-component composite NTB z-score indicated less worsening ($p = 0.020$) in the antibody responder group compared with the placebo group at month 12 (see table 5). This treatment difference was also apparent at month 12 in the all-memory ($p = 0.033$) composite z-score.

The NTB composite z-scores were regressed on the geometric mean antibody titers from four groups (placebo, titers 0 to 1:99, 1:100 to 1:2,199, and ≥1:2,200). Concentration-response analysis indicated relationships between geometric mean titer and the nine-component ($p = 0.006$), all memory ($p = 0.009$), immediate memory ($p = 0.044$), and delayed memory ($p = 0.016$) composite z-scores; that is, greater improvements from baseline in these NTB z-scores were associated with higher IgG antibody titers. The concentration-response relationship between geometric mean titer and the executive function composite z-score was not significant ($p = 0.107$), although the direction of the trend favored higher IgG antibody titers.

CSF tau and Aβ42. In the subset of antibody responders (n = 11) and placebo recipients (n = 10) who had baseline and post-baseline CSF samples, mean (± SD) baseline CSF levels of microtubule-associated tau protein were similar (740 ± 243 for antibody responders vs 811 ± 368 pg/mL for placebo; $p = 0.605$). A marginal difference in CSF Aβ42 was observed between antibody responders and placebo recipients at baseline (588 ± 119 vs 469 ± 152 pg/mL; $p = 0.059$). Baseline CSF tau and Aβ42 were within the expected ranges for patients diagnosed with probable AD.[20] CSF tau in antibody responders was reduced compared with baseline (−204 ± 57 pg/mL), and the change was greater than in the placebo group (42 ± 52 pg/mL; $p < 0.001$) (figure 3). Treatment with AN1792(QS-21) had no effect on CSF levels of Aβ42.

Discussion. AN1792(QS-21) dosing in this double-blind, placebo-controlled, multicenter, phase IIa study was discontinued after some patients developed meningoencephalitis.[8] However, the study was amended to reflect the discontinuation of dosing with an emphasis on safety, tolerability, and immunogenicity of AN1792(QS-21) as the major study objectives and the double blind and all testing procedures

Table 4 Effect of AN1792(QS-21) or placebo on exploratory measures in the efficacy-evaluable population

	Baseline		Month 12			
	n	Observed mean (SD)	n	Observed mean change* from baseline (SD)	Difference† in adjusted mean (95% CI)	*p* Value
Alzheimer's Disease Assessment Scale—Cognitive subscale						
Placebo	65	23.9 (9.9)	53	−2.7 (6.5)		
Responder	55	21.7 (9.6)	44	−3.8 (7.8)	−0.7 (−3.5, 2.2)	0.641
Disability Assessment for Dementia						
Placebo	65	74.6 (19.4)	53	−12.6 (16.0)		
Responder	55	78.9 (18.9)	43	−10.8 (17.4)	−2.3 (−9.1, 4.4)	0.491
Clinical Dementia Rating						
Placebo	65	1.06 (0.45)	53	−0.27 (0.49)		
Responder	55	0.92 (0.45)	44	−0.39 (0.50)	−0.09 (−0.29, 0.11)	0.381
Mini-Mental State Examination						
Placebo	65	20.3 (3.6)	51	−1.8 (3.7)		
Responder	55	20.7 (3.3)	42	−1.5 (3.2)	−0.3 (−1.8, 1.1)	0.678
Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change‡						
Placebo	—	—	53	4.6 (1.1)	—	
Responder	—	—	44	4.9 (1.1)	—	0.241

Patients were considered antibody responders if they had a serum anti-AN1792 IgG (total) titer ≥1:2200 at any time after injection 1. Data were analyzed using analysis of covariance.

* Negative values indicate a worsening in cognitive function.
† Placebo minus responder.
‡ Values reported are actual mean scores at month 12, *p* value is reported from the Cochran-Mantel-Haenszel mean score test.

were continued for at least 9 months after the last injection. The predefined serum antibody response (anti-AN1792 IgG titer ≥1:2,200) was achieved in almost 20% of the 300 patients receiving active treatment, even though dosing was discontinued after only one to three injections.

There were no differences between antibody responder and placebo groups in the exploratory measurements of cognitive and disability scores (ADAS–Cog, DAD, CDR, MMSE, and ADCS–CGIC distributions). The placebo group showed a lower than expected mean annual decline on the ADAS–Cog (2.7 points) and MMSE (1.8 points), which would have been predicted from prior clinical trials in patients with mild to moderate AD over 1 year,[21-23] and such a small decline in the placebo group would have affected the results of the between-group comparisons. Despite the absence of significant effects in the analyses of cognitive and functional measures, the nine-component NTB z-score analysis revealed a positive signal, indicating less worsening of performance in antibody responders when compared with the placebo group. The most noteworthy finding was an improvement in the memory domain of the NTB. Moreover, greater improvements from baseline were associated with higher IgG antibody titers for the overall composite NTB z-score, as well as for all memory, immediate memory, and delayed memory composite NTB z-scores.

In the small subset of antibody responders with post-baseline CSF samples (n = 11), there was a significant decline of tau and no change in Aβ levels compared with placebo (n = 10) treatment. The decline of tau may indicate a reduced rate of cellular degeneration in antibody responders; however, these findings must be interpreted cautiously, since the subset was small. The subgroup of antibody responders with a post-baseline CSF evaluation had differences in baseline and demographic characteristics from the whole group of antibody responders (data not shown), hence this small group may not be representative.

Treatment-related AEs occurred more commonly in those treated with AN1792(QS-21) than placebo, and were generally of mild to moderate intensity. The percentage of patients who died was similar between active- and placebo-treated patients. Only one patient, an antibody nonresponder, died of an AE (cerebral infarction) thought to be related to administration of AN1792(QS-21). Severe treatment-related AEs occurred in 8% of patients who received active treatment (over half of which were associated with encephalitis) and in no patients who received placebo. All 18 patients who reported meningoenceph-

Table 5 *Effect of AN1792(QS-21) or placebo on neuropsychological test battery measures in the efficacy-evaluable population*

	Baseline		Month 12			
	n	Observed mean (SD)	n	Observed mean change from baseline (SD)	Difference* in adjusted mean (95% CI)	*p* Value
Wechsler Memory Visual—Immediate						
Placebo	64	5.23 (3.72)	46	−0.41 (3.77)		
Responder	55	4.73 (2.63)	35	0.66 (3.42)	−0.61 (−2.12, 0.89)	0.418
Wechsler Memory Visual—Delayed						
Placebo	63	2.00 (1.69)	45	−0.33 (1.51)		
Responder	55	1.93 (1.60)	34	0.21 (1.79)	−0.43 (−1.09, 0.24)	0.203
Wechsler Memory Verbal—Immediate						
Placebo	65	7.94 (4.70)	48	−0.23 (3.30)		
Responder	55	8.24 (4.43)	37	0.68 (3.36)	−0.90 (−2.35, 0.55)	0.220
Wechsler Memory Verbal—Delayed						
Placebo	64	2.73 (2.13)	48	−0.31 (1.53)		
Responder	55	2.42 (1.92)	37	0.46 (1.46)	−0.66 (−1.31, −0.01)	0.047
Rey Auditory Verbal Learning—Immediate						
Placebo	64	22.42 (11.01)	48	−2.25 (7.73)		
Responder	55	24.20 (9.58)	40	−0.28 (7.46)	−2.48 (−5.67, 0.70)	0.125
Rey Auditory Verbal Learning—Delayed						
Placebo	63	9.27 (5.28)	48	−1.33 (6.02)		
Responder	54	8.74 (5.58)	38	−0.11 (3.62)	−0.74 (−2.81, 1.33)	0.479
Wechsler Memory—Digit Span						
Placebo	65	9.89 (4.18)	51	−1.22 (2.02)		
Responder	55	10.31 (3.45)	41	−0.56 (2.76)	−0.82 (−1.79, 0.14)	0.094
Controlled Word Association Test						
Placebo	65	21.54 (12.31)	52	−2.90 (5.99)		
Responder	55	23.07 (11.81)	41	−2.10 (6.95)	−1.01 (−3.64, 1.62)	0.449
Category Naming Test						
Placebo	65	8.09 (5.42)	52	−1.00 (3.72)		
Responder	55	9.31 (4.37)	41	−0.76 (3.58)	−0.81 (−2.23, 0.60)	0.257
Nine-component composite z-score						
Placebo	64	0.08 (0.77)	48	−0.20 (0.45)		
Responder	55	0.11 (0.61)	36	0.03 (0.37)	−0.23 (−0.41, −0.04)	0.020
All memory composite z-score						
Placebo	64	0.13 (0.85)	48	−0.17 (0.60)		
Responder	55	0.10 (0.69)	36	0.11 (0.44)	−0.27 (−0.51, −0.02)	0.033
Immediate memory composite z-score						
Placebo	64	0.08 (0.92)	48	−0.12 (0.69)		
Responder	55	0.10 (77.8)	36	0.12 (0.49)	−0.24 (−0.51, 0.04)	0.092
Delayed memory composite z-score						
Placebo	64	0.19 (0.86)	48	−0.21 (0.67)		
Responder	55	0.10 (0.80)	36	0.10 (0.59)	−0.27 (−0.55, 0.01)	0.062
Executive function composite z-score						
Placebo	64	−0.02 (0.90)	48	−0.25 (0.42)		
Responder	55	0.14 (0.78)	36	−0.12 (0.52)	−0.17 (−0.38, 0.04)	0.120

Patients were considered antibody responders if they had a serum anti-AN1792 IgG (total) titer ≥1:2200 at any time after injection 1. Data were analyzed using analysis of covariance. Negative values for the difference in the mean change indicate a tendency for antibody responders to perform better than placebo patients.

* Placebo minus responder.

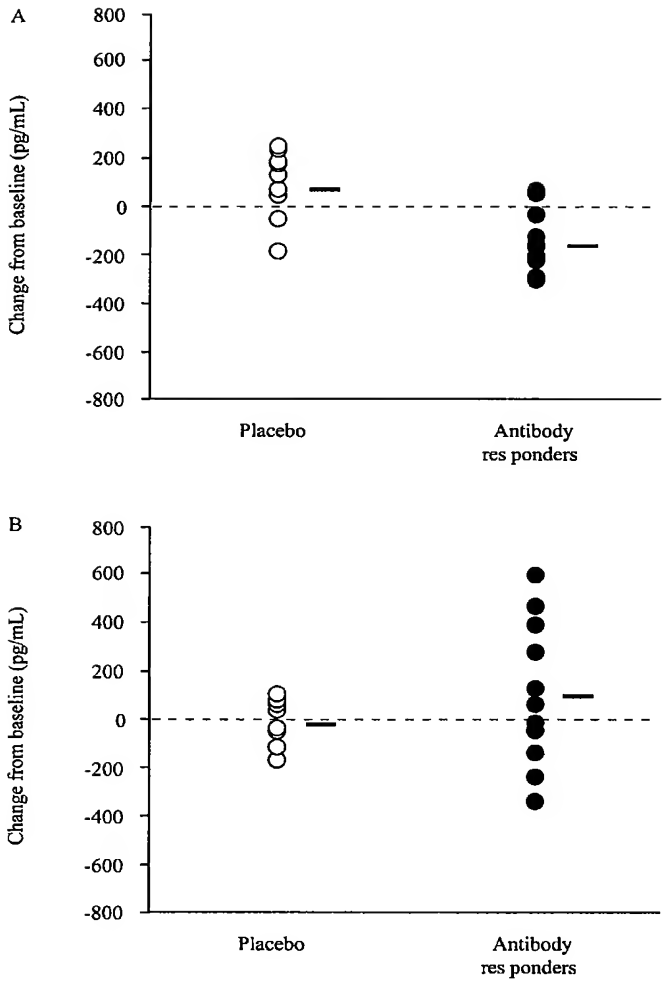

Figure 3. Change from baseline in CSF tau and Aβ42 in the efficacy-evaluable population of patients with baseline and post-baseline lumbar punctures. (A) CSF tau; (B) CSF Aβ42. Baseline levels of CSF tau and Aβ42 did not differ significantly between antibody responder (n = 11) and placebo (n = 10) groups. Data presented are raw mean (horizontal bar) and individual subject (symbol) changes from baseline.

alitis received AN1792(QS-21). There were no differences in baseline or demographic characteristics between patients who developed meningoencephalitis and those who did not. Although the patients who developed meningoencephalitis mounted higher mean serum anti-AN1792 IgG titers than others in the active treatment group, titers were highly variable and only 13 of the 18 patients developed the prespecified titers of >1:2,200. In addition, one meningoencephalitis patient had serum IgG titers of <1:50 throughout the study.

Prior to initiation of this study, there was no indication of meningoencephalitis in any preclinical investigations or during the phase I studies. A change in the AN1792(QS-21) formulation may have resulted in this complication. During the phase I trial polysorbate-80 was added to the formulation to prevent AN1792(QS-21) from precipitating out of solution.[7] This new formulation, which did not show toxicity in experimental animals, was used for injections 5 to 8 in the phase I trial and in all patients immunized in the phase IIa trial. In retrospect, one patient in the phase I study probably developed meningoencephalitis approximately 6 weeks after receiving the new formulation as the fifth immunization; however, at the time a diagnosis of a CNS neoplasm was made. This patient subsequently died from pulmonary embolism almost 1 year after the last dose of study drug, and the diagnosis of meningoencephalitis was made at autopsy. Neuropathologic examination of the brain demonstrated depletion of neocortical amyloid from the brain without evidence of a neoplasm. In addition, the presence of a T-cell meningoencephalitis[24] was noted, suggesting that activation of these T-cells may be responsible for the inflammatory response. Both of these observations, depletion of brain amyloid and T-cell activation, were noted in another postmortem examination of a patient who participated in this phase IIa study.[18]

Preliminary analysis has raised the possibility that the change of formulation (addition of polysorbate-80) was instrumental in the development of the inflammatory reaction, possibly by exposing greater numbers of amino acids in the Aβ1–42 peptide to epitopes responsible for mounting inflammatory T-cell responses.[25] These findings suggest that meningoencephalitis may be related to the induction of a T-cell response, rather than to the development of antibodies.[25]

These findings suggest that the development of meningoencephalitis may not be related to the antibody level per se, and that other immunologic mechanisms may be responsible for this complication. Furthermore, the findings suggest that the potentially beneficial effects of immunization may not be accompanied with the risk of meningoencephalitis.

Findings have been reported from a single study site with a subset of 30 patients who received study drug immunization as part of this phase IIa trial.[26] In this subset analysis, antibody-positivity was defined using a tissue amyloid plaque immunoreactivity assay, and it was observed that the antibody positive group performed better than the antibody negative group on the MMSE, DAD, and the WMVis-D subtest of the NTB. While our present analysis of the entire cohort of patients who received AN1792(QS-21) and developed anti-AN1792 IgG titer ≥1:2,200 vs placebo is suggestive of a cognitive benefit for the treated group, our analysis does not confirm the specific findings of the single site subset analysis.

As performance of serologic assays at this single investigative site[26,27] may have unblinded this site during the study, we analyzed the full study data excluding patients from this site. The cohort analysis with or without patients from this single site was essentially the same. There are many differences between the single site analysis[26] and the one pre-

sented here that may account for the inconsistencies between them. The studies used different methods to measure antibody responses, and in the present study, comparisons of cognitive functioning were made between antibody responders and placebo-treated patients rather than classifying all patients as either responders or nonresponders based on tissue immunoreactivity. These differences, plus the small sample size (n = 30),[26] seems to be the most likely explanation for the discrepancies.

Although dosing in this trial was interrupted after fewer immunizations than were scheduled because of the occurrence of meningoencephalitis in a small percentage of immunized patients, the results offer promise for Aβ immunotherapy as a potential means of treating AD. The results showed significant effects in antibody responders upon some memory functions as measured on the NTB, and the decreased CSF tau levels suggest a downstream neuropathologic benefit of targeting Aβ. Together with postmortem reports of depleted neocortical Aβ in AN1792(QS-21)-treated patients,[18] the findings of this trial suggest that Aβ immunotherapy may be useful for the treatment of AD.

Acknowledgment

Christoph Hock, University of Zurich, Switzerland, also served as an investigator in this study.

Appendix

The AN1792(QS-21)-201 Study Team principal investigators are as follows: Rafeal Blesa, Hospital San Pablo y Santa Cruz, Barcelona, Spain; Mercè Boada Rovira, Fundació ACE, Institut Català de Neurociències Aplicades, Barcelona, Spain; Jody Corey-Bloom, AD Research Center, La Jolla, CA; Jean-François Dartigues, Hôpital Pellegrin–Tripode, Bordeaux, France; Rachelle Doody, Baylor College of Medicine, Houston, TX; Bruno Dubois, Hôpital La Pitié Salpêtrière, Paris, France; Larry Eisner, Baumel-Eisner Neuromedical Institute, Fort Lauderdale, FL; Stephen Flitman, Xenoscience Inc., Phoenix, AZ; Françoise Forette, Hôpital BROCA–La Rochefoucauld, Paris, France; Ana Frank Garcia, Hospital Universitario La Paz, Madrid, Spain; Daniel Grosz, Pharmacology Research Institute, Northridge, CA; Pierre Jouanny, Hôtel Dieu–CHU, Rennes, France; Louis Kirby, Pivotal Research Centers, Peoria, AZ; Bernard Laurent, Hôpital Bellevue, Saint-Etienne, France; Bernard Michel, Hôpital Sainte-Marguerite, Marseille, France; Florence Pasquier, Hôpital Roger Salengro, Lille, France; Jordi Pena-Casanova, Hospital del Mar, Barcelona, Spain; Ronald Petersen, Mayo Clinic, Rochester, MN; José Manuel Ribera Casado, Hospital Clinico San Carlos, Madrid, Spain; Ralph Richter, Clinical Pharmaceutical Trials, Inc., Tulsa, OK; Martin Rossor, National Hospital for Neurology and Neurosurgery, London, UK; Jacques Touchon, Hôpital Gui de Chaulliac, Montpellier, France; Bruno Vellas, CHU La Grave–Casselardit, Toulouse, France; Parvaneh Zolnouni, CA Clinical Trials, Beverly Hills, CA.

References

1. Games D, Adams D, Alessandrini R, et al. Alzheimer-type neuropathology in transgenic mice overexpressing V717F β-amyloid precursor protein. Nature 1995;373:523–527.
2. Schenk D, Barbour R, Dunn W, et al. Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse. Nature 1999;400:173–177. Letter.
3. Morgan D, Diamond DM, Gottschall PE, et al. Aβ peptide vaccination prevents memory loss in an animal model of Alzheimer's disease. Nature 2000;408:982–985. Letter.
4. Janus C, Pearson J, McLaurin J, et al. Aβ peptide immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease. Nature 2000;408:979–982. Letter.
5. DeMattos RB, Bales KR, Cummins DJ, Dodart JC, Paul SM, Holtzman DM. Peripheral anti-Aβ antibody alters CNS and plasma Aβ clearance and decreases brain Aβ burden in a mouse model of Alzheimer's disease. Proc Natl Acad Sci USA 2001;98:8850–8855.
6. McLaurin J, Cecal R, Kierstead ME, et al. Therapeutically effective antibodies against amyloid-beta peptide target amyloid-beta residues 4–10 and inhibit cytotoxicity and fibrillogenesis. Nat Med 2002;8:1263–1269.
7. Bayer AJ, Bullock R, Jones RW, et al. Evaluation of the safety and immunogenicity of synthetic Aß42 (AN1792) in patients with AD. Neurology 2005;64:94–101.
8. Orgogozo J-M, Gilman S, Dartigues J-F, et al. Subacute meningoencephalitis in a subset of patients with AD after Aβ42 immunization. Neurology 2003;61:46–54.
9. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34:939–944.
10. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
11. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects [online]. Available at: http://www.wma.net/e/policy/b3.htm#paragraphe29. Accessed May 27, 2004.
12. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356–1364.
13. Schneider LS, Olin JT, Doody RS, et al. Validity and reliability of the Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997;11 Suppl 2:S22–S32.
14. Gauthier S, Gelinas I, Gauthier L. Functional disability in Alzheimer's disease. Int Psychogeriatr 1997;9 Suppl 1:163–165.
15. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412–2414.
16. Galasko D, Chang L, Motter R, et al. High cerebrospinal fluid tau and low amyloid β42 levels in the clinical diagnosis of Alzheimer disease and relation to apolipoprotein E genotype. Arch Neurol 1998;55:937–945.
17. Fox NC, Cousens S, Scahill R, Harvey RJ, Rossor MN. Using serial registered brain magnetic resonance imaging to measure disease progression in Alzheimer disease. Arch Neurol 2000;57:339–344.
18. Ferrer I, Boada Rovira M, Sanchez Guerra ML, Rey MJ, Costa-Jussá F. Neuropathology and pathogenesis of encephalitis following amyloid-beta immunization in Alzheimer's disease. Brain Pathol 2004;14:11–20.
19. Masliah E, Hansen L, Adame A, et al. Abeta vaccination effects on plaque pathology in the absence of encephalitis in Alzheimer's disease. Neurology 2005;64:129–131.
20. Andreasen N, Gottfries J, Vanmechelen E, et al. Evaluation of CSF biomarkers for axonal and neuronal degeneration, gliosis, and beta-amyloid metabolism in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2001;71:557–558.
21. Thal LJ, Grundman M, Berg J, et al. Idebenone treatment fails to slow cognitive decline in Alzheimer's disease. Neurology 2003;61:1498–1502.
22. Aisen PS, Schafer KA, Grundman M, et al. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. JAMA 2003;289:2819–2826.
23. Schneider LS. Assessing outcomes in Alzheimer disease. Alzheimer Dis Assoc Disord 2001;15 Suppl 1:S8–S18.
24. Nicoll JAR, Wilkinson D, Holmes C, Steart P, Markham H, Weller RO. Neuropathology of human Alzheimer disease after immunization with amyloid-β peptide: a case report. Nat Med 2003;9:448–452.
25. Pride MW, Black RW, Hagen M, et al. Evaluation of the cellular immune response in AD patients after immunotherapy with AN1792(QS-21). Poster 201.14. Presented at the 33rd meeting of the Society for Neuroscience; New Orleans, LA; November 8–12, 2003. Abstract available online at http://sfn.scholarone.com.
26. Hock C, Konietzko U, Streffer JR, et al. Antibodies against beta-amyloid slow cognitive decline in Alzheimer's disease. Neuron 2003;38: 547–554.
27. Hock C, Konietzko U, Papassotiropoulos A, et al. Generation of antibodies specific for beta-amyloid by vaccination of patients with Alzheimer disease. Nat Med 2002;8:1270–1275.